(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 8 November 2001 (08.11.2001)

PCT

(10) International Publication Number WO 01/82981 A1

(51) International Patent Classification⁷: A61K 38/28, A61M 11/00

A61L 9/04,

(21) International Application Number: PCT/US01/00038

(22) International Filing Date: 2 January 2001 (02.01.2001)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/201,238 09/702,460 1 May 2000 (01.05.2000) US 31 October 2000 (31.10.2000) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



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A MEDICINAL AEROSOL FORMULATION

This application claims priority from U.S. provisional application Serial No. 60/201,238 filed May 1, 2000, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

5 Field of the Invention

This invention relates to a medicinal aerosol formulation, and more particularly, to a medicinal aerosol formulation comprising a troglitazone.

Description of the Related Art

Delivery of drugs to the lung by way of inhalation is an important means of treating a variety of conditions, including such common local conditions as 10 cystic fibrosis, pneumonia, bronchial asthma and chronic obstructive pulmonary disease and some systemic conditions, including hormone replacement, pain management, immune deficiency, erythropoiesis, diabetes, etc. Anti-diabetic drugs, e.g. an insulin, are among the drugs that are administered to the lung for such 15 purposes. Such drugs are commonly administered to the lung in the form of an aerosol of particles of respirable size (less than about 10 µm in diameter). The aerosol formulation can be presented as a liquid or a dry powder. In order to assure proper particle size in a liquid aerosol, particles can be prepared in respirable size and then incorporated into a colloidial dispersion either containing a propellant as a 20 metered dose inhaler (MDI) or air, such as in the case of a dry powder inhaler (DPI). Alternatively, formulations can be prepared in solution form in order to avoid the concern for proper particle size in the formulation. Solution formulations must nevertheless be dispensed in a manner that produces particles or droplets of respirable size.

For MDI application, once prepared an aerosol formulation is filled into an aerosol canister equipped with a metered dose valve. In the hands of the patient the formulation is dispensed via an actuator adapted to direct the dose from the valve to the patient.

What is needed and desired is a stable aerosol formulation for the treatment of diabetes and conditions related thereto.

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SUMMARY OF THE INVENTION

It has surprisingly been found that a novel and stable medicinal aerosol formulation of an anti-diabetic or hypoglycemic medicament can be obtained without the use of a surfactant, such as sorbitan trioleate. The medicament is rosiglitazone and its salts or esters, such as, for example, maleate, hydrochloride, etc., or other pharmaceutically acceptable forms. This medicament may be used alone or combined with a suitable β -cell hypoglycemic selected from the group consisting of an amylin and an insulin; as well as other medicament agents possessing antidiabetic activity, including the α -cell hypoglycemic glucagon, acetohexamide, chlorpropamide, tolazamide, tolbutamide, and glipizide, as well as any mixture of any two or three of the foregoing β -cell hypoglycemic medicaments.

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DETAILED DESCRIPTION OF THE INVENTION

This application makes reference to U.S. Application Serial No. 09/209,228 filed December 10, 1998, which is incorporated hereinto by reference in its entirety.

This invention involves a stable aerosol formulation suitable for delivery which comprises (a) a troglitazone, e.g. its hydrochloride, medicament and (b) a suitable fluid carrier. The troglitazone, e.g. its hydrochloride, may be present as a single drug or in combination with a suitable β -cell hypoglycemic, such as an amylin and an insulin and their derivatives, and the α -cell hypoglycemic glucagon.

A suitable β-cell hypoglycemic medicament is one selected from either an amylin or an insulin and any of their derivatives. A suitable synthetic, antidiabetic agent is one selected from an acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, etc., and a mixture of any two or three of the foregoing medicaments.

The term "insulin" shall be interpreted to encompass natural extracted human insulin, recombinantly produced human insulin, insulin extracted from bovine and/or porcine sources, recombinantly produced porcine and bovine insulin and mixtures of any of these insulin products. The term is intended to encompass the polypeptide normally used in the treatment of diabetics in a substantially purified form but encompasses the use of the term in its commercially available

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pharmaceutical form, which includes additional excipients. The insulin is preferably recombinantly produced and may be dehydrated (completely dried) or in solution.

The terms "insulin analog," "monomeric insulin" and the like are used interchangeably herein and are intended to encompass any form of "insulin" as defined above wherein one or more of the amino acids within the polypeptide chain has been replaced with an alternative amino acid and/or wherein one or more of the amino acids has been deleted or wherein one or more additional amino acids has been added to the polypeptide chain or amino acid sequences which act as insulin in decreasing blood glucose levels. In general, the "insulin analogs" of the present invention include "insulin lispro analogs," as disclosed in U.S. Pat. No. 5,547,929, incorporated hereinto by reference in its entirety, insulin analogs including LysPro insulin and humalog insulin, and other "super insulin analogs", wherein the ability of the insulin analog to affect serum glucose levels is substantially enhanced as compared with conventional insulin as well as hepatoselective insulin analogs which are more active in the liver than in adipose tissue. Preferred analogs are monomeric insulin analogs, which are insulin-like compounds used for the same general purpose as insulin, such as insulin lispro, i.e., compounds which are administered to reduce blood glucose levels.

An "amylin" includes natural human amylin, bovine, porcine, rat,
rabbit amylin, as well as synthetic, semi-synthetic or recombinant amylin or amylin
analogs, including pramlintide and other amylin agonists, as disclosed in U.S. Patent
No. 5,686,411, and U.S. Patent No. 5,854,215, both of which are incorporated
hereinto by reference in their entirety.

For purposes of the formulations of this invention, which are
intended for inhalation into the lungs, the troglitazone, e.g. its hydrochloride,
medicament and the other medicaments (when present) are préferably micronized
whereby a therapeutically effective amount or fraction (e.g. ninety percent or more)
of the medicament is particulate. Typically, the particles have a diameter of less
than about 10 microns, and preferably less than about 5 microns, in order that the
particles can be inhaled into the respiratory tract and/or lungs.

The particulate troglitazone, e.g. troglitazone hydrochloride, medicament or drug is present in the inventive formulations in a therapeutically

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effective amount, that is, an amount such that the drug can be administered as a dispersion or an aerosol, such as topically, or via oral or nasal inhalation, and cause its desired therapeutic effect, typically preferred with one dose, or through several doses. The troglitazone medicament is administered as an aerosol from a conventional valve, e.g., a metered dose valve, through an aerosol adapter also known as an actuator.

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The term "amount" as used herein refers to quantity or to concentration as appropriate to the context. The amount of the troglitazone medicament or mixture of medicaments, including troglitazone hydrochloride, that constitutes a therapeutically effective amount varies according to factors such as the potency of the particular medicament or medicaments used, the route of administration of the formulation, and the mechanical system used to administer the formulation. A therapeutically effective amount of troglitazone, alone or combined, can be selected by those of ordinary skill in the art with due consideration of such factors. Generally a therapeutically effective amount of troglitazone will be from about 0.001 parts by weight to about 5 parts by weight based on 100 parts by weight of the fluid carrier e.g. propellant.

A suitable fluid carrier is selected. A suitable fluid carrier includes air, a hydrocarbon, such as n-butane, propane, isopentane, etc. or a propellant. A suitable propellant is any fluorocarbon, e.g. a 1-6 hydrogen containing flurocarbon, such as CHF₂CHF₂, CF₃CH₂F, CH₂F₂CH₃ and CF₃CHFCF₃; a perfluorocarbon, e.g. a 1-4 carbon perfluorocarbon, such as CF₃CF₃, CF₃CF₂CF₃; or any mixture of the foregoing, having a sufficient vapor pressure to render them effective as propellants. Some typical suitable propellants include conventional chlorofluorocarbon (CFC) propellants such as propellants 11, 12 and 114 or a mixture of any of the foregoing propellants. Non-CFC propellants such as 1,1,1,2-tetrafluoroethane (Propellant 134a), 1,1,1,2,3,3,3-heptafluoropropane (Propellant 227) or mixtures thereof are preferred. The propellant is preferably present in an amount sufficient to propel a plurality of the selected doses of the drug from an aerosol canister.

Optionally, a suitable stabilizer is selected. A suitable stabilizer is a "water addition". As used herein a "water addition" is an amount of water which (1) is added, either initially with other components of the aerosol formulation, e.g. the

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troglitazone hydrochloride medicament and fluid carrier, or after the other components, e.g. medicament, fluid carrier, are combined and processed, (2) is in addition to the water which is always present and which develops during processing and/or storage of the aerosol formulation, i.e. "developed" or "nascent" formulation water, and (3) is present in an amount which further stabilizes a medicinal aerosol formulation, e.g. troglitazone hydrochloride, water.

An aerosol formulation preferably comprises the water addition in an amount effective to more effectively stabilize the formulation relative to an identical formulation not containing the water addition, i.e. containing only nascent formulation water, such that the drug e.g., troglitazone hydrochloride, does not settle, cream or flocculate after agitation so quickly as to prevent reproducible dosing of the drug. Reproducible dosing can be achieved if the formulation retains a substantially uniform drug concentration for about fifteen seconds to about five minutes after agitation.

The particular amount of the water addition that constitutes an effective amount is dependent upon the particular fluid carrier, e.g. propellant, and on the particular drug or drugs used in the formulation. It is therefore not practical to enumerate specific effective amounts for use with specific formulations of the invention, but such amounts can readily be determined by those skilled in the art with due consideration of the factors set forth above. Generally, however, the water addition must be present in a formulation in an amount in excess of the concentration of the nascent formulation water. Such concentration of nascent formulation water typically ranges up to 300 parts by weight per one million parts by weight of the total weight of the aerosol formulation. Accordingly, the water addition in excess of this nascent water concentration typically ranges from about 10 parts by weight to 5000 parts by weight per one million parts by weight of the total aerosol formulation weight. Most preferred is that the concentration of the water addition in excess of this nascent water concentration is from 500 parts by weight to 5000 parts by weight per one million parts by weight of the total weight of the medicinal aerosol formulation.

It is to be emphasized that this is an amount which exceeds the amount of nascent or developed formulation water. It is also to be stressed that

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preferably this amount of water addition can be added and initially combined with the other components of the formulation, e.g. medicament such as troglitazone hydrochloride, and fluid carrier, e.g. 1,1,1,2-tetrahydrofluoroethane. However, the water addition can be added to the resultant formulation after these other components have been processed, e.g. prior to or subsequent to storage.

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It has surprisingly been found that the troglitazone formulation of the invention is stable without the necessity of employing a cosolvent, such as ethanol, or surfactants. However, further components, such as conventional lubricants or surfactants, cosolvents, ethanol, etc., can also be present in an aerosol formulation of the invention in suitable amounts readily determined by those skilled in the art. In this regard, reference is made to U.S. Patent No. 5,225,183, which is incorporated hereinto by reference in its entirety. Typically, a co-solvent such as ethanol is added in an amount ranging from 0.5 to 10% by weight of the total weight of the formulation.

A most preferred formulation comprises the troglitazone medicament, the fluid carrier, the cosolvent and the water addition, for example, troglitazone hydrochloride, 1,1,1,2-tetrafluoroethane, ethanol and the water addition.

Generally the formulations of the invention can be prepared by combining (i) the troglitazone drug, e.g. troglitazone hydrochloride drug, in an amount sufficient to provide a plurality of therapeutically effective doses; (ii) the fluid, e.g. propellant, in an amount sufficient to propel a plurality of doses, e.g. from an aerosol canister; (iii) optionally, the water addition in an amount effective to further stabilize each of the formulations; and (iv) any further optional components e.g. ethanol as a cosolvent; and dispersing the components. The components can be dispersed using a conventional mixer or homogenizer, by shaking, or by ultrasonic energy as well as by the use of a bead mill or a microfluidizer. Bulk formulations can be transferred to smaller individual aerosol vials by using valve to valve transfer methods, pressure filling or by using conventional cold-fill methods. It is not required that a component used in a suspension aerosol formulation be soluble in the fluid carrier, e.g. propellant. Those that are not sufficiently soluble can be coated onto the drug particles in an appropriate amount and the coated particles can then be incorporated in a formulation as described above.

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Aerosol canisters equipped with conventional valves, preferably metered dose valves, can be used to deliver the formulations of the invention. It has been found, however, that selection of appropriate valve assemblies for use with aerosol formulations is dependent upon the particular component and other 5 adjuvants used (if any), on the fluid, e.g. propellant, and on the particular drug being used. Conventional neoprene and buna valve rubbers used in metered dose valves for delivering conventional CFC formulations often have less than optimal valve delivery characteristics and ease of operation when used with formulations containing HFC-134a or HFC-227. Therefore certain formulations of the invention 10 are preferably dispensed via a valve assembly wherein the diaphragm is made of a nitrile rubber such as DB-218 (American Gasket and Rubber, Schiller Park, Ill.) or an EPDM rubber such as Vistalon™ (Exxon), Royalene™ (UniRoyal), bunaEP (Baver). Also suitable are diaphragms fashioned by extrusion, injection molding or compression molding from a thermoplastic elastomeric material such as FLEXOMERTM GERS 1085 NT polyolefin (Union Carbide). 15

Conventional aerosol canisters, coated or uncoated, anodized or unanodized, e.g., those of aluminum, glass, stainless steel, polybutyl or polyethylene terephthalate, and coated canisters or cans with epon, epoxy, etc., can be used to contain a formulation of the invention.

The formulation of the invention can be delivered to the respiratory tract and/or lung by oral inhalation in order to treat diabetes and a diabetes related condition susceptible of treatment by inhalation. The formulations of the invention can also be delivered by nasal inhalation in order to treat, e.g., diabetes (systemic), or they can be delivered via oral (e.g., buccal) administration in order to treat, e.g., diabetes and a diabetes related condition.

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We claim:

- 1. A medicinal aerosol formulation, which comprises:
- (a) a therapeutically effective amount of a troglitazone medicament; and
- (b) a fluid carrier.
- 2. The formulation as defined in claim 1 wherein said medicament is troglitazone hydrochloride combined with a second medicament selected from the group consisting of an amylin, an insulin a suitable synthetic anti-diabetic agent and a mixture of the foregoing.
- The formulations as defined in claim 2 where the second medicament further comprises a suitable synthetic antidiabetic agent.
 - 4. The formulation as defined in claim 3 wherein said agent is selected from the group consisting of glucagon, acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, and a mixture of any of the foregoing agents.
 - 5. The formulation as defined in claim 2 wherein said second medicament comprises an amylin.
 - 6. The formulation as defined in claim 2 wherein said second medicament comprises an insulin.
- 7. The formulation as defined in claim 4 wherein said second medicament comprises glucagon.
 - 8. The formulation as defined in claim 1 wherein said fluid carrier is selected from the group of propellants consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or a mixture thereof.
- 9. The formulation as defined in claim 1 which said fluid carrier is a compressed gas selected from the group consisting of air, carbon dioxide, nitrogen, and a mixture of and of the foregoing compressed gases.
 - 10. The formulation as defined in claim 1 wherein said fluid carrier is a hydrocarbon selected from the group consisting of n-butane, propane, isopentane and a mixture of any of the foregoing hydrocarbons.

- 11. The formulation as defined in claim 1 which further comprises a stabilizer comprising a water addition present in an amount which is in addition to nascent formulation water.
- 12. The formulation as defined in claim 1 which further includes 5 a cosolvent.
 - 13. The formulation as defined in claim 12 where said cosolvent comprises ethanol.
 - 14. The formulation as defined in claim 1 wherein said medicament comprises troglitazone hydrochloride.
- 15. A method of preparing a medicinal aerosol formulation according to claim 1, which comprises:
 - (a) combining (i) said troglitazone medicament in an amount sufficient to provide a plurality of therapeutically effective doses and (ii) said fluid carrier in an amount sufficient to propel a plurality of said therapeutically effective doses from an aerosol canister; and
 - (b) dispersing components (i), and (ii).
 - 16. The method as defined in claim 15 which further comprises combining in step (a), (iii) a stabilizer in an effective stabilizing amount and in step (b) dispersing components (i) and (ii) with said stabilizer.
- 20 17. The method as defined in claim 16 which further comprises combining in step (a) a cosolvent and in step (b) dispersing components (i), (ii) and (iii) with said cosolvent.
 - 18. The method as defined in claim 17 wherein said cosolvent is ethanol.
- 19. A method of treating or controlling in a human or an animal diabetes or a diabetes related condition capable of treatment or control by oral or nasal inhalation, which comprises, administering a formulation according to claim 1 to said human or animal by oral or nasal inhalation.
- 20. A formulation according to claim 1 in an aerosol canister equipped with a metered dose valve.
 - 21. A metered dose inhaler containing a medicinal aerosol formulation, the formulation comprising:

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- (a) a troglitazone drug in particulate form in a therapeutically effective amount;
 - (b) a fluid carrier; and
- (c) a stabilizer comprising a water addition which is present in an amount which (1) is in excess of nascent formulation water and (2) is present in an amount to stabilize the formulation to prevent settling, creaming or flocculation for a time sufficient to allow reproducible dosing of said troglitazone drug after agitation of the formulation.
- 22. The metered dose inhaler as defined in claim 21 wherein said stabilizer is present in said excess in an amount of about 10 parts by weight to about 5000 parts by weight based on one million parts by total weight of the medicinal aerosol formulation.
 - 23. The metered dose inhaler as defined in claim 21 wherein said troglitazone drug is combined with a second drug selected from the group consisting of an amylin, an insulin and a mixture of the foregoing.
 - 24. The metered dose inhaler as defined in claim 23 which further comprises a suitable antidiabetic medicament.
 - 25. The metered dose inhaler as defined in claim 24 wherein said medicament is selected from the group consisting of glucagon, acetohexaminde, tolbutamide, glipizide, glyburide, glucophage, phentolamine, and a mixture of any of the foregoing medicaments.
 - 26. The metered dose inhaler as defined in claim 23 wherein said β -cell hypoglycemic comprises an amylin.
- 27. The metered dose inhaler as defined in claim 23 wherein said
 25 β-cell hypoglycemic comprises insulin.
 - 28. The metered dose inhaler as defined in claim 23 which further comprises glucagon.
 - 29. The metered dose inhaler as defined in claim 28 wherein said β-cell hypoglycemic comprises a mixture of an amylin, insulin and glucagon.
- 30. The metered dose inhaler as defined in claim 23 wherein said fluid carrier is a propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or a mixture thereof.

- 31. The metered dose inhaler as defined in claim 23 wherein said fluid carrier is a hydrocarbon selected from the group consisting of n-butane, propane, isopentane and a mixture of any of the foregoing hydrocarbons.
- 32. The metered dose inhaler as defined in claim 23 wherein said formulation further includes a cosolvent.
 - 33. The metered dose inhaler as defined in claim 32 wherein said cosolvent is ethanol.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/00038

	A. CLASSIFICATION OF SUBJECT MATTER				
IPC(7) : A61L 9/04; A61K 38/28; A61M 11/00					
US CL : 424/45; 514/4; 128/200.14					
According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIEL	DS SEARCHED				
Minimum documentation searched (classification system followed by classification symbols) U.S.: 424/1.11, 43, 44, 45, 94.1; 514/3, 4, 866, 970; 128, 200.14, 200.21, 200.23					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet					
C. DOC	UMENTS CONSIDERED TO BE RELEVANT		· · · · · · · · · · · · · · · · · · ·		
Category *	Citation of document, with indication, where a	ppropriate, of the relevant passages	Relevant to claim No.		
X00Y	US 5,998,463 A (HULIN et al) 07 December 1999 col. 6, lines 34-68, col. 7 lines 1-68, col. 8, lines 1-46, claims, abstract.	(07.12.99), see col. 5, lines 29-64.	1-7, 11-13, 19 0		
Y	EVANS et al, Recent Developments and Emerging Mellitus, Drugs R&D. 1999, Vol. 2, No. 2, pages	Therapies for Type 2 Diabetes 75-94, see abstract.	1-7, 14, 20, 23-29		
Y	REASNER, C. A., II. Promising New Approaches Suppl. 1, pages S41-S48, see abstract.	. Diabetes, Obes. Metab. 1999, Vol. 1,	1-7, 14, 20, 23-29		
Y	US 5,744,123 A (AKEHURST et al.) 28 April 1998 col. 3, lines 3-65.	8 (28.04.98) see col. 2, lines 5-60,	8-10, 14-33		
Y, P .	US 6,136,294 A (ADJEI, et al.) 24 October 2000 (24.10.2000) see entire document.	8-10, 12-13, 14-33		
		·	İ		
Purther documents are listed in the continuation of Box C. See patent family annex.					
• S	pecial categories of cited documents:	"T" later document published after the inter	national filing date or priority		
	date and not in conflict with the application but cited to underst document defining the general state of the art which is not considered to be principle or theory underlying the invention		ntion		
"B" earlier application or patent published on or after the international filing date		"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone			
establish (specified)		"Y" document of particular relevance; the considered to involve an inventive step combined with one or more other such	when the document is		
O document	referring to an oral disclosure, use, exhibition or other means	being obvious to a person skilled in the	art		
P document published prior to the international filing date but later than the priority date claimed		"&" document member of the same patent family			
Date of the actual completion of the international search 27 April 2001 (27.04.01) Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Date of mailing of the international search report Authorized officer Clinton Ostrup					
27 April 2001 (27.04.01) 4 4 AUG 2001			700 ZUUT		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Authorized officer					
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Washington, D.C. 20231 Facsimile No. (703)305-3230		Telephone No. (703) 308-1235	U		

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/00038

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)				
This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:				
1.		Claim Nos.: because they relate to subject matter not required to be searched by this Authority, namely:		
2.		Claim Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:		
3.	6.4(a).	Claim Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule		
Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)				
This International Searching Authority found multiple inventions in this international application, as follows: Please See Continuation Sheet				
1. 2.		As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite		
3.		payment of any additional fee. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:		
	·			
4.		No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:		
Ren	nark on	Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/00038

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING: This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

I Group I, claims 1-14, is drawn to a formulation.

Group II, claims 15-18, is drawn to a method making the formulation of Group I.

Group III, claim 19, is drawn to a method of use for the formulation of Group I.

**B Group IV, claims 20-33, is drawn to an apparatus to dispense the formulation of Group I.

The inventions listed as Groups I, II, III, and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature for the following reasons: the common special technical feature of each of these inventions is the formulation of claim 1. However, since the formulation of claim 1 is not novel, a common special technical feature does not exist between the four inventions. Claim 1 describes a formulation comprising the medicament troglitazone and a fluid carrier, however, this combination is commonly used to treat Type II Diabetes. See: col. 17 lines 1-3 and col. 18 lines 35-47.

Continuation of B. FIELDS SEARCHED Item3: Data Bases: EAST, WEST, STN, CAPLUS Search Terms: troglitazone, carrier, amylin, inhaler, aerosol, insulin, glucagon

Form PCT/ISA/210 (extra sheet) (July 1998)